## PATENT SPECIFICATION

(11) **1 588 933** 

(21) Application No. 28818/77

(22) Filed 8 July 1977

(44) Complete Specification published 29 April 1981

(51) INT CL3 A61N 1/00 1/04 1/30//A61F 13/00

(52) Index at acceptance

A5R 85E1 85E2 85F1 BF



## (54) DRESSINGS FOR USE ON A MAMMALIAN BODY AND CAPABLE OF FORMING A GALVANIC COUPLE THEREWITH

I, MAURICE SEIDERMAN, a citizen of the United States of America of 3306 Deronda Drive, Hollywood, California 90068, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention relates to dressings for use on a wound or lesion on a

mammalian body and capable of forming a galvanic couple therewith.

The need to provide protection for a wound, lesion or the like on an animal body during the healing thereof has long been recognized. Bandages, surgical dressings and coatings are often used for this purpose. More recently, surgical grafting techniques have been developed to avoid the oxygen impermeability problems encountered with extensive use of bandage-like protective coatings. Although skin grafting is quite successful when the patient's own skin is used, grafts from donors often give rise to rejection problems preventing the proper therapeutic effects. Thus, other proteinaceous materials such as collagen have been employed in oxygen-permeable protective materials.

In recognition of the highly favorable, inherent characteristics of collagen which render it adaptable for providing protective films for wounds, lesions and the like, I have developed a process for the formation of adherent films disclosed in my U.S. Patent Specification No. 3,563,228 issued February 16, 1971. Briefly described, that earlier patent relates to the application of an electric field, of

suitable polarity, to a dispersion of undenatured collagen fibrils to cause electrochemical-linking between the fibrils of the dispersion. The collagen, thus applied, is also capable of linking to native collagen fibrils exposed at the wound site to effect a highly adherent protective surface thereover.

In recognizing the advance over the prior art provided by my U.S. Patent Specification No. 3,563,228, it would be desirable to provide these adherent, skinlike protective coatings but without the need for application of an external power source to provide the iontophoretic impetus therefor, it being appreciated that the electric apparatus are often bulky and, oftentimes require the patient to be treated at some central location. Accordingly, it is desirable to be able to provide these

protective coatings by continuous treatment of the patient without significant restrictions upon ambulation or the necessity of confinement.

Further along these lines, the utility of an electric field in medical treatment is, of course well known. For example, it has been commonplace to provide bandagelike articles with electrodes comprising dissimilar metallic materials to create a galvanic cell for various types of clinical treatment. These articles, conventionally termed voltaic plasters, have been devised for the iontopheric administration of certain medicaments through a patient's skin. Note, for example, United States Patent Specification Nos. 116,562, No. 175,974, No. 222,276, No. 393,741 and No. 1,967,927.

The prior art voltaic plasters suffer numerous significant disadvantages, however. Perhaps the most important are the tendencies towards metal poisoning and/or for electrode burns due to the materials employed, chiefly based upon copper and zinc as the dissimilar materials for the galvanic cell.

Currently, when it is desired to iontophoretically administer topical medicaments, external power sources are employed. Note, e.g. United States

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	Patent Specification No. 3,163,166, as well as my earlier United States Patent Specification No. 3,563,228.	
	Moreover, all prior art methods based upon the application of an electric field to the hody have hitherto employed substantial voltages and/or currents which not	
5	only tend to be discomforting to the patient, but can actually traumatize the area proximate the point of application.	5
	Consequently, it is most desirable to provide a therapeutic iontopheric	
	treatment of mammalian bodies which optimizes the healing effect thereof while minimizing the highly deleterious side effects and eliminating the need for bulky	
10	external nower sources.	10
	According to one feature of the present invention there is provided a dressing	
	adapted for application to a mammalian body having a wound or lesion, the said dressing comprising: (a) a dressing substrate adapted for application to the said	
	body. (b) a single metallic electrode; and (c) collagen and/or an ionizable or polar	15
15	medicament in electrically co-operative relationship with the electrode: the face of the electrode remote from the said substrate being arranged such that in use at least	13
	part thereof directly contacts the body, the said dressing being capable in use of	
•	forming a galvanic couple between the said single electrode and the body when the dressing is applied over the wound or lesion and producing, without use of an	
20	external power source, a local current effective for iontophoresis whereby the	20
	collagen or medicament is caused to contact or migrate within the wound or lesion. According to one particular embodiment the dressing according to the present	
	invention may include a film-forming quantity of collagen fibrils whereby in use an	
25	adherent skin-like protective membrane of the collagen fibrils electrochemically-linked to exposed collagen fibrils of the wound or lesion may be obtained. The	25
23	collagen fibrils may, for example, be present in the form of a paste dispersion which	
	is desirably isotonic in character and optionally possesses selected metallic salts corresponding to those found in the animal body and present in similar minute	
	proportions to provide an electrolyte for the conduction of an electrical current.	20
30	The collagen paste dispersion may if desired be impregnated in the substrate.  When such a collagen dispersion is disposed proximate to a wound or lesion on	30
	the animal hody to be treated, an electric field will be established between the	
	dispersion and the underlying area of tissue which exhibits a net effective negative electrical characteristic.	
35	Surprisingly, it has also been acertained that ionizable or polar medicaments	35
	may be effectively administered to a mammalian body using the dressing of the invention to provide an iontophoretic impetus derived, in part, from the naturally-	
	occurring local charges on the body to be treated in concert with the compatible	
40	electrode of the dressing itself. If desired the dressing may include collagen as described above whereby a collagen film is formed at the same time as	40
40	administration of medicament. The dressing according to the invention is	
	efficacious for the administration of any ionizable or polar medicament responsive to an electric field; proteinaceous medicaments, or derivatives thereof, being	
	preferred. The proteinaceous medicaments may be either undenatured or	
45	denatured e.g. the protein component of mild or strong silver protein and	45
	alginates. Additionally, there may be present various metallic salts or compounds, particularly when a denatured protein is employed. The most preferred metallic ion	
	is silver but other medicinally-effective metallic ions may be incorporated.	
50	The dressing according to the invention employed to deliver the medicament to the mammalian body has an integral electrode of, e.g., foil in electrically-	50
••.	cooperative relationship with the medicament thereon. Aluminum is the most	
	preferred electrode material; however, the electrode may be fabricated from any of a number of known metallic materials.	
	When the device, comprising the electrode and medicament, is applied to a	55
55	mammalian body, natural body fluids or, optionally, administrated isotonic or other electrolytic fluids, will establish the appropriate electric current and concomitant	,,
	field for delivery of the medicament deep within the wound, lesion, or the like, on	
	the body. The medicaments envisioned for use in conjunction with this invention comprise, but are not limited to, anti-infective, analgesic, bacteriostatic, and like	
60	ionizable or polar compounds, provided the compound is responsive, in terms of	60
	migration, to an electric field.  Fig. 1 is a bottom elevation view of a dressing according to an embodiment of	
	the present invention; and	
65	Fig. 2 is a side elevation view of the dressing of Fig. 1. In order to more fully illustrate the present invention, the following detailed	65

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description will be given in terms of a preferred embodiment and exemplified with respect thereto. The same is intended, however, to be illustrative and in no wise Furthermore, as used in the context of the present invention, the term dressing is meant to include all varieties of surgical dressings, regardless of physical 5 5 configuration, which may be applied over a wound site to effect treatment therefor. Thus, the present invention envisions utility extending from the rather small adhesive bandages to large dressings of several square feet which may be applied to burn victims. The collagen dispersion for use in the dressing according to the invention may, 10 10 for example, be prepared in the same manner as that described in U.S. Patent Specification No. 3,563,228, save for the fact that the collagen concentration in the instant dispersion is greater than the preferred 0.25% to 1% by weight concentration recited therein, e.g., up to about 50% by weight concentration, but most desirably having the consistency of soft table butter. More specifically, the 15 15 instant collagen suspension may be prepared from bovine deep flexor tendon which has been cleaned and trimmed of fat and other extraneous matter, frozen, and subsequently sliced perpendicular to the longitudinal axis of the tendons to a suitable length of about 0.001 mm to 0.5 mm, preferably from 0.2 mm to 0.5 mm, albeit such a length is not critical. The collagen fibrils may then be disaggregated by 20 20 treatment with proteolytic enzyme such as commercial ficin. This treatment may be achieved, for example, by gentle agitation for approximately 1 hour at 35°F in an aqueous solution of ficin. These fibrils are then washed with distilled water and treated with aqueous sodium chloride solution of approximately 1% by weight concentration for about 1 hour in two or three successive treatments (see U.S. 25 Patent Specification No. 3,563,228). Having thus been prepared, these fibrils may 25 then be added to a mixture of equal parts of ethanol and water, optionally containing approximately 0.2% cyanoacetic acid if long-term storage is anticipated; this mixture may then be agitated at a temperature approaching the freezing point thereof and subsequently homogenized by a conventional homogenizer. 30 30 Optionally, the collagen dispersion may be produced according to the teachings of either U.S. Patent Specification No. 3,368,911 or the process of Battista as described in the Journal of Applied Polymer Science, 11, 41-498 (1967). Such a dispersion of, for example, 10% by weight collagen concentration, will exhibit a paste-like or syrupy consistency, sometimes similar to that of soft butter. 35 35 This paste or dispersion may then be enhanced for better conductivity by additions of saline (usually in amounts ranging from between 0.1% to 1.0% by weight), such as sodium chloride or potassium chloride or a mixture thereof, preferably in amounts to render the paste isotonic; that is, 0.9%. Metallic salts corresponding to those indigenous to the animal body may also be added in similar minute quantities, 40 40 e.g. in amounts ranging between about 0.01% and 10% by weight. Selection of these salts, specifically to be rich in positive ions, is well within the purview of the skilled The most preferred embodiment in accordance with the present invention is illustrated in Figures 1 and 2. In Figure 1, there is shown a dressing generally 45 45 designated as 40 bearing an area 42 which is a film of metallic material. Borne upon the film 42 is a film of collagen 44. The electrical potential is derived from a single active electrode, 42, which is in contact with the skin of the patient to be treated proximate the wound area. The electrode 42 is chosen to ensure it possesses negative electrical characteristics with respect to the collagen film, as shown in 50 50 The materials' selection for electrode 42 is restricted primarily upon considerations such as standard reduction potential to ensure the electrode maintains a negative potential with respect to the collagen film; the propensity for dissolution, to minimize the introduction of the electrode material within the 55 55 wound area, as well as other considerations well known to the skilled artisan Preferred electrode materials are, for example, aluminum, mild silver protein and zinc. However, when zinc is employed, due to its galvanic activity, it is preferable to form electrode 42 as a narrow strip adjacent collagen film 44, in contradistinction to the film shown in Figure 1, wherein the electrode is adjacent 60 60 the entire periphery of collagen film 44. Particularly beneficial results may be realized upon employing a mild silver protein film for electrode 42. Mild silver protein, a colloidal solution prepared by the interaction of protein and silver oxide and containing about 19 to 23% by weight silver, is a well known bacteriostatic agent. Only a small fraction of the 65 65

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5	silver is in an ionizable state and, thus, mild a fact, is somewhat demulcent. For a more compand effects of mild silver protein, see Goodma Basis of Therapeutics, 3rd Edition, McMillan, The mild silver protein membrane may propensity to disintegrate in moisture or, with occurrence. Accordingly, the electrode mater	prehensive understanding of the uses an and Gillman. The Pharmacological 1969.  y be fabricated to exhibit either a good wet strength to preclude such	5
10	the healing process.  Another of the preferred electrode minocuous material with little tendency to diss A dressing similar to that depicted in Figur experimentation. The dressing 40 has an up conveniently possesses a pressure sensitive as	naterials is aluminum, a relatively solve when the dressing is employed. The 2 was fabricated for purposes of per, liquid impervious layer 46 and	10
15	side in order to facilitate adherence of the dre test employed a conventional bandage c trademark Curad. A thin foil of aluminum, for was adhered over a gauze area 50 of the banda in accordance with the process described abo	essing to the area for treatment. This ommercially marketed under the example, 0.002 to 0.003 inches thick, ge. A paste of collagen was prepared we and deposited over the electrode	15
20	42 by means of a doctor blade. The collar supported or unsupported, and may be processor insoluble in water, as desired. Once the configure 2, a drop of saline solution was Potentiometric tests were performed upon the	sed to yield the collagen dispersible dressing was assembled as shown in placed upon the collagen film, dressing at that time and indicated a	20
25	voltage of 0.5 volts between the electrode and microamperes.  Other dressings were fabricated in sir materials as set forth in Table I. The voltage these dressings is likewise set forth in Table	nilar fashion employing electrode and current developed by each of	25
	TABLE I		
30	Electrode Material         Voltage           Aluminum         0.5           Zinc         1.2           Tin         0.5           Titanium         0.1	400 200 50	30
35	Tantalum 0.1	* 2.5	35
	*reverse polarity  It has been observed that the collagen of substrate electrochemically-links in a very influence of the electrical potential derived fi	short amount of time under the rom the galvanic source. Moreover,	
40	the collagen film adherently and tenaciously both mechanical and chemical linkages with the of the wound. Accordingly, it has further been be removed in a relatively short amount of adherent, skin-like collagen film. Moreover, it	ne exposed, damaged collagen fibrils observed that the dressing itself may f time, leaving behind this highly	40
45	film thus applied to the wound site, upon somewhat and tend to close the wound in a benefits, are realized upon application of mate undergoing treatment and, accordingly, reject	limited dehydration, will contract natural manner. These, and other rials totally acceptable to the animal tion is rare.	45
50	Moreover, various modifications may be dressing of the present invention. For example with the collagen dispersion to form a paste of Further, the conductivity of mild silver protein fine spray or mist of ammonia prior to use. T	e, mild silver protein may be mixed fenhanced electrochemical activity. has been found to be enhanced by a	50
55	between the electrode and the collagen film is in order that the dressing be adapted for tailor- true as the electrochemical-linking phenomen potential and may be advanced or retarded b It has also been determined that the notab	capable of a wide range of selection made operation. This is particularly on is a strong function of electrical based upon materials selection.	55
60	invention may be realized by impregnating e tissue paper with the appropriate collagen dis rather than depositing the collagen upon a co impregnated paper, whether readily disintegrat	either the substrate itself or simple spersion, with or without additions, onventional dressing substrate. The	60

<u> </u>	1,300,233	
	then be utilized in the dressing of the invention. In like vein, the collagen dispersion, with or without additions, may be dried to a film, supported or unsupported, and used without need of a separate substrate. These embodiments	
5	may prove highly beneficial for treatment of extensive wound areas such as, for example, burns.  Also, the collagen film may be electrically linked prior to its application to the wound area. Thus, the pre-linked film or membrane may be placed over the area to	5
10	the collagen membrane and damaged collagen fibrils of the wound.  It is observed that prior art voltaic plasters suffer numerous disadvantages, the	10
	most significant being risk of metal poisoning and/or electrode burns to the body being treated due to the construction of the bandage from highly active dissimilar metals as the galvanic electrode materials, and an inability to effectively deliver a wide range of medicinally effective medicaments. Both of these significant	
15	drawbacks may be reduced or avoided by the present invention, which provides in one embodiment an integral electrode on a bandage substrate having a quantity of medicament also borne thereon. When applied to a mammalian body, natural body fluids or applied isotonic fluids will create a voltaic effect whereby the medicament	15
20 .	pharmacologic response.  In part, the improvement derived from the present invention is coupled with	20
	the recognition that a mammalian body possesses a slight, inherent negative electric charge, particularly at areas proximate the site of the wound or lesion. Thus, by appropriate design of a delivery device, materials may be employed which advantageously utilize this electrical characteristic thereby overcoming the need	25
25	for dissimilar electrodes to effect the galvanic cell while yet providing for the generation of a suitable electric field for the iontophoretic impetus. The improvement in the iontophoretic administration of medicaments using a dressing	
30	of the present invention lies also, in part, in administering a broad range of ionizable or polar medicaments responsive to the applied electric field.  While numerous anionic, cationic, and polar medicaments, including certain amphoteric medicaments, are envisioned within the scope of the present invention,	30
35	the preferred are proteinaceous medicaments, either undenatured or denatured. Thus, these preferred medicaments include, for example, the protein component of mild or strong silver protein, and alginates. Additionally, various effective metallic salts may be employed in this iontophoretic administration method in conjunction with the protein or derivative thereof. It has been determined that the	35
40 '	proteinaceous medicament may be employed alone when the protein component is not denatured. When, however, that protein component is denatured, it is particularly beneficial to employ a metallic salt, most preferably a silver salt. However, other medicinally-effective equivalent metallic salts might be utilized. Likewise other medicaments including, particularly, Dexamethasone Sodium	40
45	Phosphate, Methylprednisolone Sodium Succinate, Flurandrenolide, and Amphotericin, are preferred compounds for use in conjunction with the present invention. These compounds may be employed individually or in admixture, with or without the additional presence of metallic salts, or denatured or undenatured mild silver proteins. Moreover, for example various steroids, antibiotics and	45
50	antifungal compounds may also be employed, together or separately as might be desired. Further medicinally-effective compounds and preparations may be selected from specific pharmacological effects, such selection being within the scope of those skilled in the art.  The most preferred proteinaceous medicament is the antiseptically-effective	50
55	mild silver protein, which is a colloid of silver with protein, containing on the order of about 10 to 25% by weight silver. This material is readily available, commercially; and is described in "The Merck Index", Merck & Co., Inc., 5th Edition, 1940, page 458. However, other anti-infectious, analgesic and bacteriostatic proteinaceous compounds may, for example, be employed to this	55
60	end.  In electrically-cooperative relationship with the medicament is an electrode, which may assume any of a number of physical configurations. Most preferably it is	60
	a metallic foil, although any suitable metallic material may be utilized and may be deposited in the form of a liquid such as, for example, dispersion, and subsequently dried. The electrode material should be selected from those known to be compatible with the mammalian body for the obvious reasons including e.g.	
65	toxicity and irritation. As will become more apparent hereinbelow, a salient	65

5	distinction between the dressing of the present invention and those of the prior art is the absence of a galvanic couple of active metallic components on the bandage substrate to which has been attributed the significant problems of electrode burns and/or metal poisoning indigenous to the latter. That is, the dressing of the present invention employs but a single metallic material for the electrode, regardless of the physical state or configuration thereof, i.e., a dressing such as illustrated in Figures	5
10 .	I and 2.  The most preferred electrode is a foil of aluminum metal. Other electrode materials include, for example, copper, zinc, tin, and titanium, each of which will provide an effective positive charge with respect to the mammalian body. Should the medicament utilized require a net negative charge to provide the desired iontopheric impetus of proper polarity, such materials as tantalum might be utilized.	10
15	Regardless of the electrode material or configuration thereof, it is essential that the electrode be in electrically-cooperative relationship with the medicament to be iontophoretically administered. As a consequence, when the dressing is activated by electrolytic fluids such as, for example, body fluids or administered isotonic saline, voltaic interaction will establish an electric field between the	15
20	electrode and underlying wound site and generate a corresponding electric current, whereby the medicament is caused to migrate deeply within the wound in response thereto.  The present invention envisions utility extending from small adhesive dressings	20
25	to large dressing of several square feet which may be applied to, for example, burn victims. Exemplary of a particularly suitable dressing is that of Figure 1, denoted generally as 40, which comprises, e.g., a 6"×2" substrate 46, having a medial portion and terminal portions. The medial portion has adhered thereto a foil of, for	25
30	example, aluminum metal, denoted as 42. The foil optimally comprises approximately one half of the total surface area of the dressing substrate; however, these dimensions are not critical provided the electrode material has sufficient surface area to provide the required iontophoretic-effective electric current.	30
50	The central portion of the electrode 42 has coated thereon, or adhered thereto, a quantity of the desired medicament 44. Preferably, the medicament is applied as a paste or liquid to some absorbent material such as sterile tissue paper or sterile cloth or gauze. The medicament is allowed to dry and the porous carrier	
35	adhered to the foil electrode.  An optional embodiment employs a commercially-available surgical bandage, such as those marketed under the trademark "Curad". As opposed to the dressing of Figure 1, which may be made in relatively large dimensions, and wherein the	35
40	terminal portions may or may not be coated with an adhesive substance, this alternate embodiment is designed for application to, for example, rather small cuts or abrasions. The dressing comprises a plastics or polymeric substrate having a medial portion and adhesively coated end portions with an absorbent gauze adhered to the substrate in the medial portion. Two foil electrodes are also borne	40
45	upon the substrate and are caused to partially overlap the medial gauze area. The desired medicament may be applied to the gauze pad and allowed to dry.  A dressing in accordance with this latter embodiment was prepared in order to ascertain the effectiveness of the iontophoretic administration of mild silver protein to a human body. The dressing employed is approximately 7.5 cm long and 2.5 cm	45
50	wide. The gauze pad accounts for approximately 30% of the total surface area of the dressing and is coated with a solution of mild silver protein (USP) made isotonic with 0.9% by weight sodium chloride. After the medicament has dried, two rectangular strips of aluminum foil having dimensions of about 2.5 cm×2.0 cm are adhered to the dressing substrate, partially overlapping the coated gauze area such	50
55	that approximately 15% of each aluminum foil strip is in direct contact with the coated gauze pad.	55
55	This dressing was placed on a human body over a minor wound. A drop of isotonic saline was administered to the coated gauze pad in order to establish voltaic action between the aluminum foil electrodes and the body. The electric potential was measured to be about 3/4 of a volt, and the current generated about	
60	10 microamperes. In response to the electric field thus generated, the silver protein medicament migrated deeply within the wound at a rate much greater than were the electric field absent.  A similar dressing was prepared employing as a substrate, a commercially-	60
65	available bandage, marketed under the name "Air-Vent Tape Clear", by Johnson & Johnson. This bandage, measuring about 9.0 cm×2.6 cm, was placed with the	65

being borne upon the substrate within the said medial portion and supporting a discrete quantity of ionizable or polar medicament within its peripheral dimensions, the electrode presenting sufficient surface area for direct contact with

the body to establish an iontophoretically-effective electric current between the medicament and the body to cause migration of the medicament into the wound or

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lesion thereon.

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5	11. A dressing as claimed in any one of claims 1 to 9 wherein the substrate comprises a medial portion bounded by terminal portions, ionizable or polar medicament being borne upon the substrate within the medial portion, the electrode being borne on at least one of the terminal portions and partially overlapping the medial portion in electrically-cooperative relationship with the medicament.	5
10	12. A dressing as claimed in any one of the preceding claims wherein the medicament is absorbed within a carrier selected from sterile paper, sterile cloth and hydrogel polymers, the said carrier being adhered to the dressing.  13. A dressing as claimed in claim 1 further including an electrochemically-effective quantity of an electrolyte.  14. A dressing as claimed in claim 13 wherein the electrolyte is sodium	10
15	chloride, potassium chloride or a mixture thereof.  15. A dressing as claimed in any one of claims 1 to 3, 13 and 14 including a filmforming quantity of collagen fibrils so as to obtain in use an adherent skin-like protective membrane of the collagen fibrils electrochemically-linked to exposed collagen fibrils of the wound or lesion.	15
20	16. A dressing as claimed in claim 15 wherein the collagen fibrils are present in the form of a paste dispersion supported by the substrate and containing an electrolyte.  17. A dressing as claimed in claim 16 wherein the collagen dispersion is coated on the substrate.	20
25	18. A dressing as claimed in claim 16 wherein the collagen dispersion is impregnated in the substrate.  19. A dressing as claimed in any one of claims 16 to 18 wherein the collagen dispersion is dried.  20. A dressing as claimed in claim 15 wherein the metallic electrode is in the	25
30	form of a metallic film upon which the collagen fibrils are borne in electrically co- operative relationship such that, in use, upon introduction of fluid to the dressing, a galvanic current is generated whereby the collagen fibrils electrochemically link to form the adherent, skin-like protective membrane.  21. A dressing as claimed in claim 20 further including mild silver protein	30
35	mixed with the collagen fibrils.  22. A dressing as claimed in claim 20 wherein the metallic electrode is mild silver protein.  23. A dressing as claimed in claim 1 substantially as herein described.  24. A dressing as claimed in claim 1 substantially as herein described with reference to the drawings.	35

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COMPLETE SPECIFICATION

1 SHEET

This drawing is a reproduction of the Original on a reduced scale

